STUDIES IN THE CYCLOHEPTANE SERIES. VI

Synthesis of Spiro (6.2) nonane- 1.2- and Spiro (6.3) decane- 1.3-dicarboxylic Acids

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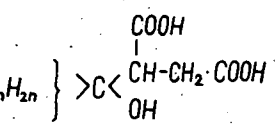
ω-imide of cycloheptane- 1.1 -dicyano- 1.1 -diacetic acid on bromination and subsequent treatment with formic acid gave the bridged imide which when subjected to a series of other reactions furnished spiro (6.2) nonane- 1.2 -dicarboxylic acid. Treatment of the ω-imide with methylene iodide gave spiro (6.3) decane- 1.3 -dyciano- 1.3 -dicarboxylic acid imide which on hydrolysis and subsequent decarboxylation gave a mixture of cis-and trans-spiro (6.3) decane- 1.3 -dicarboxylic acid.

Earlier interest in the Chemistry of spiro-compounds started mainly with the advent of the Valency-deflexion hypothesis advanced by THORPE and INGOLD. To test the validity of this BEESLEY, INGOLD and THORPE [1] started with the argument that if the ring size was gradually increased, the external angle would also decrease and the two external valencies would come closer and this could be detectable by the ease of formation and stability of a cyclopropane ring. Their results indicated that the cyclohexane ring confers stability upon the cyclopropane ring while the gem-dimethyl group does not. Later work of BECKER and THORPE [2], DESHPANDE and THORPE [3] and BIRCH, GOUGH and KON [4] led to the same conclusions.

The turning point in the Valency-deflexion hypothesis started with the work of BIRCH and THORPE [5], who carried out similar types of reactions with various ketones, e. g. diethyl ketone, methyl n-hexyl ketone, methylbenzyl ketone, cyclopentanone and 3-and 4-methylcyclohexanones. The cyclopropane derivatives analogous to the cyclohexane and its dimethyl derivatives obtained from the above ketones did not show the stability of the cyclohexane analogues as the cyclopropane ring would easily break on hydrolysis to give the hydroxy acids of the type (I):



I.

The observation that the mere addition of a methyl group to the cyclohexane ring could reduce the stability of the compounds puzzled the workers considerably

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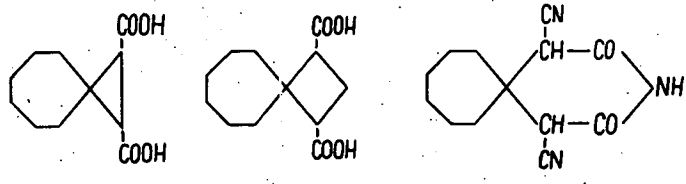
and this lowered their belief in the Valency-deflexion hypothesis and faith in the strainless character of the rings became more acceptable.

The effect of the cycloheptane ring on the stability of the cyclopropane ring was examined by BAKER and INGOLD [6] and as a result of their studies they came to the conclusion that in the cyclophetane ring system there existed some conditions whereby the strain of the ring was reduced, as the effect of the cycloheptane ring in promoting the formation and enhancing the stability of the spiran structure was not only less than what it might be expected to be, but was actually less than what the cyclohexane ring was known to exert. The stability of the spirane structure was reported to be midway between that of the cyclohexane and cyclopentane analogues.

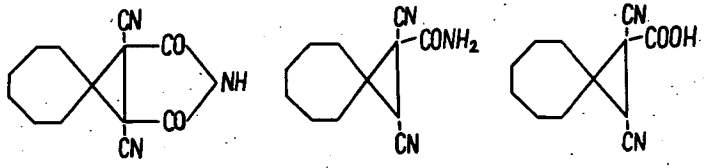
The above studies of the spiranes and the modern knowledge regarding the configuration of the rings reveal one fundamental point that, though the strain due to the non-planar structure of the ring does not exist in largesized rings, yet due to spatial disposition of the atoms these rings do have a specific effect on the course of the reaction which at present cannot be predicted with any precision.

It was to study this effect that the present work on the synthesis of spiro (6.2) nonane- 1.2 -dicarboxylic acid (II) and spiro (6.3) decane- 1.3-dicarboxylic acid (III) was taken up. The procedures followed for their synthesis were those adopted by BIRCH, GOUGH and KON *(loc. cit.)* for the analogous compounds of the former and of KERR [7] and PAUL [8] for the analogues of the latter.



II. III. IV.

Starting from cyclophetanone, the GUARESCHI imide (IV) was prepared according to the method of DAY *et al.* [9]: on treatment with bromine it gave the dibromo derivative which on heating with formic acid furnished the bridged imide (V) while on boiling with one mole of potassium hydroxide for 5 minutes, spiro (6.2) nonane-

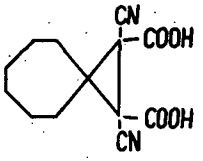


V. VI. VII.

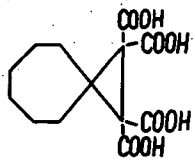
1.2-dicyano-1-carboxylic acid amide (VI) was obtained. The latter compound was then diazotised according to the conditions suggested by BIRCH *et al. (loc. cit.)* when only a gummy mass was obtained which on keeping in vacuum and triturating with benzene gave a small quantity of spiro (6.2) nonane-1.2-dicyano-1-carboxylic acid (VII). Further decarboxylation of this acid to spiro (6.2) nonane-1.2-dinitrile

and spiro (6.2) nonane-1.2-dicarboxylic acid could not be carried out due to the insufficient amount of the product (VII).

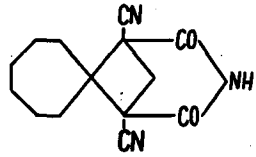
Hydrolysis of the bridged imide (V) with three molecules of alkali gave spiro (6.2) nonane-1.2-dicyano-1.2-dicarboxylic acid (VIII), which on further hydrolysis with excess of alkali gave a product, the structure of which is under investigation,



VIII.



IX.

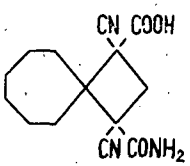


X.

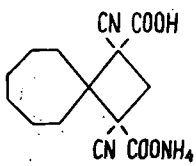
though it does not appear to be spiro (6.2) nonane-1.1.2.2-tetracarboxylic acid (IX) which it was expected to be. Similarly the hydrolysis of the compound (VI) with excess of alkali did not give the expected spiro (6.2) nonane-1.1.2-tricarboxylic acid.

For debrominating the dibrome ω-imide, formic acid was preferred to ethanol as it gave better yields of the product (V). Though the cleavage of the bridged imide (V) take place readily with a molecule of alkali with the loss of a carbon atom, the diazotisation of the amide (VI) did not give good yields. This reluctance on the part of the amide to furnish the corresponding acid on diazotisation is rather difficult to understand in view of analogous compounds having been reported to give excellent yields (BIRCH, GOUGH and KON and BIRCH and THORPE, *loc. cit.*). This resistance may probably be due to the steric effect of the ring or the reaction conditions may not be selective enough to allow the reaction to proceed, although varying conditions were employed. Diazotisation in glacial acetic acid [10] also proved equally futile and the original amide was recovered.

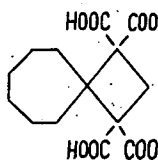
The synthesis of spiro (6.3) decane-1.3-dicarboxylic acid (III) was next carried out to study the formation and stability of the cyclobutane ring and to compare it with that of the spiro (6.2) nonane analogue. For this study the GUARESCHI imide (IV) was treated with methylene iodide in presence of sodium methoxide to furnish the spiro (6.3) decane-1.3-dicyano-1.3-dicarboxylic acid amide (X). On treating it with a molecule of alkali, it gave a mixture of products which are considered to be the hydrolysis products of spiro (6.3) decane-1.3-dicyano-1.3-dicarboxylic acid mono amide (XI) along with a small amount of the ammonium salt (XII).



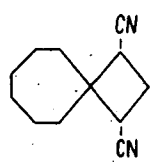
XI.



XII.



XIII.



XIV.

The compound (XI) could be obtained in pure state only in small amounts through precipitation. Hydrolysis of the product with three moles of alkali also gave a similar mixture. The imide (X) was therefore refluxed as such with excess of alkali which on acidification in the cold gave spiro (6.3) decane-1.1.3.3.-tetracarboxylic acid (XIII). The acid on decarboxylation gave a mixture of cis- and trans-spiro (6.3) decane-1.3-dicarboxylic acids (III) which were separated by refluxing with acetyl chloride for three hours when the cis-acid was converted into its anhydride and the trans-acid removed with sodium bicarbonate. Attempts to get these or their derivatives in a solid state did not meet with success.

On hydrolysing the compound (X) with three moles of alkali, a mixture of products was obtained; repeated attempts at crystallisation from anhydrous methanol gave a small ammount of a product in shining colourless flakes which analysed for spiro (6.3) decane-1.3-dinitrite (XIV). This compound was insoluble in sodium hydroxide.

Experimental

Synthesis of spiro (6.2) nonane-1.2-dicarboxylic acid. ω-Imide of α.α′-dicyano-α.α′-dibromocycloheptane-1.1-diacetic acid.

To well powdered ω-imide of α.α′-dicyanocycloheptane-1.1-diacetic acid (7,3 g) suspended in water (50 ml) contained in a flask fitted with an air condenser, bromine (4 ml) was added portion wise with vigorous shaking until a permanent orange red colour was obtained. After keeping the contents at room temperature for an hour, the bromo compound separated out as a solid which was filtered, washed and dried. Pure *ω-imide of α.α′-dicyano- α.α′-dibromocycloheptane-1.1-diacetic acid* crystallised from benzene in colourless needles had M. p.: 162 °C. (Yield: 11,0 g). Anal.: Calc.: $C_{13}H_{13}O_2N_3Br_2$ C 36,2 H 4,2; Found: C 36,4 H 4,1.

Spiro (6.2) nonane-1.2-dicyano-1.2-dicarboxylic acid imide.

The ω-imide of α.α′-dicyano-α.α′-dibromo-cycloheptane-1.1-diacetic acid (10 g) contained in a flask was suspended in water (40 ml) and formic acid (40 ml, 80%) added; the contents were slowly heated with continuous stirring to a gentle reflux and then allowed to boil for ten minutes until the entire solid dissolved. On cooling the bridged imide separated out, which was filtered at the suction; dilution of the filtrate deposited a further quantity of the imide. The combined solid was washed, dried and on crystallisation from ethanol pure *spiro (6.2) nonane-1.2-dicarboxylic acid imide* was obtained in fine colourless needles. M. p.: 210 °C. (Yield: 5,6 g). Anal.: Calc.: $C_{13}H_{13}O_2N_3$ C 64,2 H 5,4; Found: C 64,0 H 5,2.

The above imide was also obtained, though in slightly poor yield, by refluxing the dibromo acid imide with ethanol (95%).

For the preparation of larger amounts of the bridged imide, the dibromo acid imide was not isolated but formic acid was directly added to the suspension of the dibromo diacetic acid imide in water in the cold and the contents refluxed, when on cooling the bridged imide M. p.: 210° separated out.

Spiro (6.2) nonane- 1.2-dicyano-1-carboxylic acid amide.

To spiro (6.2) nonane-1.2-dicyano-1.2-dicarboxylic acid imide (6 g) contained in a flask potassium hydroxide solution (14 ml, 10%) was added and the contents refluxed for five minutes. On cooling in ice, the amide separated, which was filtered; the filtrate again boiled for five minutes when on cooling an additional quantity of the amide was obtained and the process was repeated once again to give further quantity of the amide. The combined solid was washed, dried and on crystallisation from ethanol pure *spiro- (6.2) nonane-1.2-dicyano-1-carboxylic acid amide* was obtained in fine clusters of prismatic needles. M. p.: 164—65 °C. (Yield: 4,5 g). Anal.: Calc.: $C_{12}H_{15}ON_3$ C 66,3 H 7,0; Found: C 66,1 H 7,1.

Spiro (6.2) nonane-1.2-dicyano-1.2-dicarboxylic acid.

The imide of spiro (6.2) nonane-1.2-dicyano-1.2-dicarboxylic acid (5,2 g) was dissolved in aqueous potassium hydroxide (40 ml, 10%) contained in a flask and refluxed on a sand bath for 40 minutes. The product was cooled and extracted with ether to remove any neutral organic impurities. The alkaline solution after acidification was continuously extracted with ether for three hours; the ethereal solution dried (anhydrous magnesium sulphate) and ether recovered when a solid residue was obtained. Pure *spiro (6.2) nonane-1.2-dicyano-1.2-dicarboxylic acid* was crystallised from dilute methanol in small colourless needles. M. p. 164 °C. (depressed by the spiro 6.2 nonane-1.2-dicyano-1-carboxylic acid amide. M. p.: 164 °C.) (Yield: 4,5 g). Anal.: Calc.: $C_{13}H_{14}O_4N_2 \cdot H_2O$ C 55,7 H 5,8; Found: C 55,7 H 5,6.

Spiro (6.2) nonane-1.2-dicyano-1-carboxylic acid.

Spiro (6.2) nonane-1.2-dicyano-1-carboxylic acid amide (2 g) was dissolved in cold concentrated sulphuric acid (40 ml) contained in a wide mouth boiling tube kept in an ice-bath. The contents were stirred mechanically while an ice-cold saturated solution of sodium nitrite was carefully added dropwise to avoid any frothing. The solution slowly became thicker and thicker until it looked like a solid; the addition of the nitrite solution was stopped at this point and the contents allowed to stand for 30 minutes at room temperature. Crushed ice (100 g) was then added and the reaction product continously extracted with ether for five hours. The etheric solution was dried over anhydrous magnesium sulphate and ether recovered; the residue, on keeping in vacuum, solidified and pure *spiro (6.2) nonane-1.2-dicyano-1-carboxylic acid* was crystallised from methanol in transparent cuboids. M. p.: 121 °C. Anal.: Calc.: $C_{12}H_{14}O_2N_2$ C 66,0 H 6,5; Found: C 66,0 H 6,6.

When solutions of spiro (6.2) nonane-1.2-dicyano-1-carboxylic acid amide in ethanol and sulphuric acid and glacial acetic acid were separately treated with an aqueous sodium nitrite, the above carboxylic acid was not isolated, instead the amide was recovered unchanged.

Synthesis of spiro (6.3) decane-1.3-dicarboxylic acid.
Spiro (6.3) decane-1.3-dicyano-1.3-dicarboxylic acid imide.

The ω-imide of $\alpha \cdot \alpha'$-dicyanocycloheptane-1.1-diacetic acid (8,1 g, 0,033 mol) was added to sodium methoxide (2,3 g of sodium in 35 ml methanol) contained in a flask and the contents refluxed on a water bath for 30 minutes. Methylene

iodide (13,4 g, 0.05 mol) was then added and after refluxing the reaction mixture for two hours, the contents were poured into water (75 ml) containing concentrated nitric acid (7 ml). The solid obtained was filtered, washed with ether to remove any unchanged methylene iodide and the residue on crystallisation from ethanol gave pure *spiro (6.3) decane- 1.3-dicyano-1.3-dicarboxylic acid imide* in long flat colourless needles. M. p.: 238 °C. (Yield: 5,0 g, 59%). Anal.: Calc.: $C_{14}H_{15}O_2N_3$ C 65,4 H 5,9; Found: C 65,4 H 5,8.

Partial hydrolysis of the imide of spiro (6.3) decane-1.3-dicyano-1.3-dicarboxylic acid.

(a) The above spiro-imide (5,9 g, 0,023 mol) was dissolved in aqueous potassium hydroxide (13 ml, 10%) contained in a flask and boiled under reflux for 5 minutes. The product was cooled and extracted with ether to remove any neutral impurities; the aqueous layer was acidified and the crude acid so obtained was filtered and dried which melted at 195 °C (decomp.). (Yield: 5,8 g).

Crystallisation of the product proved rather difficult; purification was, however, affected by dissolving the product in methanol and adding a large quantity of benzene when slow evaporation of methanol gave a small quantity of the pure solid, which was identified as *spiro (6.3) decane-1.2-dicyano-1.2-dicarboxylic acid monoamide.* Anal.: Calc.: $C_{14}H_{17}O_3N_3$ C 61,1 H 6,2; Found: C 61,0 H 6,1.

The product was readily soluble in water, methanol and ethanol and almost insoluble in benzene and toluene but sparingly soluble in ethyl acetate and acetone. None of these solvents proved useful for crystallisation.

(b) The spiro-imide (3.9 g, 0,015 mol) was refluxed with aqueous sodium hydroxide (20 ml, 10%) for two hours on a sand bath. The reaction product was concentrated, cooled, extracted with ether to remove any neutral impurities and the aqueous layer acidified with dilute sulphuric acid when a solid was deposited. This was filtered and dried and had M. p.: 190—5 °C (decomp.).

Attempts to crystallise from dry methanol or methanol-benzene mixture did not prove successful. However, evaporation of the solvent, instead of giving back the original solid, left a viscous residue wich solidified in vacuum. This was again dissolved in dry methanol and on keeping colourless silky flakes immediately crystallised, which melted at 182 °C. This compound was not soluble in aqueous sodium bicarbonate or hydroxide and the mixed M. p. with the original product (M. p.: 195 °C) was depressed to 160°; it was identified as the dehydrated and decarboxylated product of spiro (6.3) decane-1.3-dicyano-1.3-dicarboxylic acid. Analysis indicated that it might be *spiro- (6.3) decane-1.3-dinitrile.* Anal.: Calc.: $C_{12}H_{16}N_2$ C 76,8 H 8,5; Found: C 76,6 H 8,2.

Spiro (6.3) decane-1.1.3.3-tetracarboxylic acid.

The crude product obtained in (a) and (b) above (11.5 g) was refluxed with aqueous sodium hydroxide (200 ml, 20%) until no more ammonia was given off (5 hours). The solution was then concentrated to about 70 ml under reduced pressure, cooled, acidified and continuously extracted with ether for 30 hours. The ethereal solution was dried over anhydrous sodium sulphate and ether recovered when a residue M. p. 170—2 °C (decomp.) was obtained. (Yield: 9 g). This acid also failed

to crystallise from common solvents; however, it was purified from dry methanol-benzene mixture and had M. p.: 173 °C (decomp.). Anal.: Calc.: $C_{14}H_{18}O_8 \cdot H_2O$ C 50,6 H 6,7; Found: C 50,7 H 6,5. Eq. Wt.: Calc.: $C_{14}H_{18}O_8 \cdot H_2O$ 83,0; Found: 82,5 (potentiometric method).

Spiro (6.3) decane-1.3-dicarboxylic acids.

Spiro (6.3) decane-1.1.3.3-tetracarboxylic acid (2 g) was heated in a large boiling tube placed in an oil bath maintained at 200 °C while the product was constantly stirred, until no more carbon dioxide evolved (45 minutes). The residue was refluxed with freshly distilled acetyl chloride for 24 hours and after removing excess of the reagent, the product was taken up in ether and separated into two fractions.

The ethereal solution was washed with aqueous sodium bicarbonate (2%) and water, dried and ether recovered. The residue was obtained as a thick oil which on distillation gave the *anhydride of cis-spiro (6.3) decane-1.3-dicarboxylic acid* as a colourless liquid. B. p.: 197—9°/6 mm. Anal.: Calc.: $C_{12}H_{16}O_3$ C 69,2 H 7,7; Found: C 69,4 H 7,5.

(a) *cis-Spiro (6.3) decane-1.3-dicarboxylic acid.*

A portion of the above liquid was warmed with dilute aqueous sodium hydroxide in a water bath until no oily drops were left (3 hrs). The reaction product was cooled, acidified, continuously extracted with ether (8 hrs.), ethereal solution dried and ether recovered. A gummy residue was left which failed to solidify even on keeping in vacuum.

(b) *trans-Spiro (6.3) decane-1.3-dicarboxylic acid.*

The above aqueous sodium bicarbonate washings were acidified and continuously extracted with ether (4 hrs.). The ethereal solution was dried, ether recovered, when a gummy residue was left which resisted all attempts for solidification.

* * *

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ИССЛЕДОВАНИЯ В РЯДУ ЦИКЛОГЕПТАНА. VI

Синтез спиро (6.2) нонановой -1.2- и спиро (6.3) декановой-1.3-дикарбоновой кислот

Г. С. Сахария, Б. Р. Шарма

Бромирование ω-имида циклогептано-1.1-дициано-1.1-уксусной кислоты и после бромирования процедурой муравьиной кислоты имеет результатом спиро-имид, который подвергаясь рядам других реакций дал спиро (6.2) нонан-1.2-дикарбоновую кислоту. Процедура ω-имида метиленйодидом дала имид спиро (6.3) декан-1.3-дициано-1.3-дикарбоновой кислоты, который гидролизуясь и после этого декарбоксилироваясь дал смесь цис- и транс-видов спиро (6.3) декан-1.3-дикарбоновой кислоты.